BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

1225 Eye Street NW, Ste. 400
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January 5, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2004D-0440, Federal Register: October 4th, 2004 (Volume 69, Pages 59239-59240)

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's, the Agency's) *Draft Guidance on Computerized Systems Used in Clinical Trials.*

General Comments

In general, the September 2004 draft guidance appreciably overlaps the August 2003 guidance "Part 11, Electronic Records; Electronic Signatures – Scope and Application". Examples of sections that are similar or largely duplicated between the two guidance documents include Section IV of the September 2004 draft guidance (compared with Section III of the August 2003 guidance), Section IX-A of the draft guidance (compared

with Section III.C.3 of the August 2003 guidance), and Section XII of the draft guidance (compared to Section III.C.4 August 2003 guidance).

Some topics are presented in the September 2004 clinical trials guidance that conceivably represent valid overall recommendations in situations where electronic records or data are created, modified, maintained, archived, retrieved, or transmitted across a broader scope of regulated activities within the pharmaceutical industry. Some examples include draft guidance Sections V (Standard Operating Procedures), VI (Data Entry), X (System Controls), and XI (Training of Personnel). Information similar to that presented in these sections of the September 2004 draft guidance would be generally applicable to other areas such as research, development, manufacturing, testing, etc. but are not presented within the more general August 2003 Scope and Applications guidance.

In consideration of points above, FDA may wish to consider future management of generally-applicable guidance information within the framework of a universal guidance document (such as a revision to the August 2003 Scope and Applications document) while separately maintaining guidance unique to specific areas of activity (for example a guidance pertinent to the use of computerized systems in clinical trials).

We have a number of specific comments detailed below, with reference to particular sections of the draft guidance.

Section II. Background:

Lines 54-57, the statement indicates that "*...the primary focus of this guidance is on computerized systems used at clinical sites to collect data...*" and that "*...the principles set forth may also be appropriate for computerized systems belonging to contract research organizations, data management centers, and sponsors*". The reference to a "*primary focus*" while stating that the guidance "*...may also be applicable...*" to other situations is potentially confusing. We request clarification that the word "site" (as used throughout the guidance) primarily applies to the "clinical sites to collect data", but could also include CROs, data hosting sites (ASPs), and sponsors. We also recommend that the study sponsor's scope and responsibility be further clarified (e.g. sponsor only responsible for sponsor's supplied systems and clinical sites and CRO's be responsible for systems that they supply).

Lines 65-67, although it is clear that medical devices and lab systems are not in scope (lines 60-61) based on the guidance definition of "source documents" it seems that investigator site systems such as Hospital Information Systems, medical records, pharmacy systems, patient care systems, etc. are within the scope of the guidance. Although this language is relatively unchanged from the earlier draft guidance, it seems to expand the original intent to only apply to electronic CRF and patient diary systems (e.g. PDAs, etc.) that were being supplied by sponsors. By including all of these types of systems (which may be primarily used for non-regulated purposes) within the scope of

the guidance, we are concerned that many of these systems still do not meet the Part 11 requirements and guidance expectations. Most investigator sites are not prepared to deal with the burden of controls as set forth in this guidance (particularly computer software validation). If this guidance were strictly enforced, the result would be a greatly reduced number of qualified investigator sites. Therefore we recommend that the scope of "source documents" subject to this guidance be narrowed to the disposition of drugs (21 CFR 312.62(a)), case report forms, consent forms and patient diaries and that other clinical "supporting data" (as defined in 21 CFR 312.62(b)) be excluded from the scope of this guidance.

Section III. General Principles:
Lines 80-81, we recommend that the document retention location be *identified* within the study record rather than requiring the documentation to be *retained* within the study record.

Lines 95-96, this statement seems inconsistent with the new narrow scope interpretation of the *Guidance for Industry Part 11, ERES – Scope and Application* (February 2003), esp. Section III B. An example would be in the case of forms completed on-line, then printed and signed.

Section V. Standard Operating Procedures:
Lines 137-138, BIO generally disagrees with having SOPs on site with exceptions depending on the area of responsibility. For example it would be considered appropriate to have on site SOPs for Data Collection and Handling as well as Alternative Recording Methods (in the case of system unavailability). We recommend that the scope of this statement be clarified to include SOPs governing activities conducted at the sponsor or investigator site, as applicable.

Section VI. Data Entry, B. Audit Trails or other Security Measures:
BIO suggests that lines 189-191, dealing with the FDA's authority to copy required records on request, should reference Section XII for explanatory purposes.

Section VIII. System Security:
Lines 303-305, BIO recommends that the language be changed such that procedures and controls be implemented to prevent the data from being *altered* via external software applications that do not enter through the protective system software. We recommend that procedures and controls be implemented to prevent the data from being *browsed, queried, or reported* via external software applications that do not have appropriate security controls. The reason being that other tools (not the primary software application) such as Crystal Reports are often used to view, query or report on data contained in the database, but these tools should be prevented from altering the data.

Line 308, the addition of personnel titles seems to be a new requirement not defined within existing predicate rules. BIO recommends that "their titles" be removed from the guidance.

Line 309, BIO recommends that the cumulative record of system access privileges be recorded and maintained, but how to organize and file these records should not be prescribed (e.g. this documentation may or may not be maintained within the study documentation, and may or may not be maintained at the investigator site, but would still be available for inspection upon request).

Section IX. System Dependability:

Lines 325-327, BIO recommends a language change to indicate that, "The Agency recommends that sponsors ensure and document that all computerized systems *intended for use in the conduct of a clinical study, as documented in the study protocol and/or study agreement, be appropriately validated.*" as it would be impossible for all CROs/investigators to comply with all sponsor's "... own established requirements..." for system validation.

Line 329, is the "systems documentation" mentioned here meant to indicate validation documentation (e.g. design specification)? If so, the guidance would require the undue logistical burden of placing a full set of validation documentation for each applicable system at each investigator site. If not, we request that FDA clarify the meaning of "systems documentation" in this instance.

Line 350, BIO recommends that the term "regulated company" be defined within the definitions section of this guidance (e.g. is this term referring to the sponsor, or is this meant to include clinical sites within the definition of a "regulated company"?).

Lines 351-352, BIO understands that it would be compliant to have the documentation available at the central (sponsor's) site and made available for viewing on request at the sponsor's site. For sponsor-supplied systems, we see significant risk in sending the validation documentation to the clinical sites upon request. The documentation is generally paper-based, voluminous, and there is a risk of potential loss of or damage to original records in the transferring to the investigator sites.

Section IX. System Dependability, B. Off-the-Shelf Software:

Lines 387-388, vendors will rarely supply original design-level validation documentation to their clients due to the highly confidential and proprietary nature of these documents. Therefore, this guidance would imply that the only available option is to verify this documentation via on-site vendor audits. This seems to indicate that other possible alternative risk-based assessment methods with the potential to negate the need for an on-site audit (e.g. ISO certification, CMM certification, TickIT, PDA Tech32 reports, more extensive black box testing, etc.) would not be acceptable approaches to verifying the vendor's quality systems or products. This guidance language seems to exceed the current scope of Part 11 in that software vendor "audits" are not required (or even implied) in the current Part 11 regulation. BIO recommends that the language be revised to indicate that companies take a documented risk-based approach to software validation.

Lines 404-409, it is unlikely that the vendors will be willing to provide design-level documentation for the agency to review, as this is usually considered highly proprietary. For OTS software, it would be appropriate to have available documentation on the sponsor's intended use (e.g. user/functional requirements, system configuration). BIO recommends replacing the references to design specification with "requirements".

Definitions:

Line 544, Direct Entry: The example used within the definition of Direct Entry of "or automatic recording by the system of the output of a balance that measures subject's body weight" raises questions regarding validation. Stand-On Patient Scales (as defined within 21 CFR 880.2700) are medical devices, however the device manufacturers are exempted from 510K requirements and from the validation requirements under 21 CFR 820 for this device classification. If the manufacturer is exempt from validating the device (if computerized) then it seems inappropriate to imply that when the medical device is subsequently used to weigh patients in a clinical trial that a new validation burden would then be imposed on the sponsor and/or clinical site. BIO recommends that this second example be removed.

Line 566, Software Validation: This seems to be a new definition as the FDA's Glossary of Computerized System and Software Development Terminology states:

> *"validation, software. (NBS) Determination of the correctness of the final program or software produced from a development project with respect to the user needs and requirements. Validation is usually accomplished by verifying each stage of the software development life cycle."*

For consistency, BIO recommends using the existing definition from the FDA Glossary document.

Line 572, Source Documents: (see earlier comments for line 65-67, page 3).

In conclusion, we appreciate the opportunity to provide our comments on this draft guidance and look forward to continuing to work with the agency as it proceeds toward publication of a final guidance. If we may be of any further assistance, please do not hesitate to contact us.

Sincerely,

Sara Radcliffe

Sara Radcliffe
Managing Director
Science and Regulatory Affairs